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REVIEW

The future of disc surgery and regeneration

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Abstract

Low back and neck pain are among the top contributors for years lived with disability, causing patients to seek substantial non-operative and operative care. Intervertebral disc herniation is one of the most common spinal pathologies leading to low back pain. Patient comorbidities and other risk factors contribute to the onset and magnitude of disc herniation. Spine fusions have been the treatment of choice for disc herniation, due to the conflicting evidence on conservative treatments. However, re-operation and costs have been among the main challenges. Novel technologies including cage surface modifications, biologics, and 3D printing hold a great promise. Artificial disc replacement has demonstrated reduced rates of adjacent segment degeneration, need for additional surgery, and better outcomes. Non-invasive biological approaches are focused on cell-based therapies, with data primarily from preclinical settings. High-quality comparative studies are needed to evaluate the efficacy and safety of novel technologies and biological therapies.

Keywords Herniation · Intervertebral disc · Low back pain

Introduction

With an aging population, spine pathologies remain one of the leading causes of disability and financial burden across the globe. Low back pain was among the top five worldwide contributors of years lived with disability (YLD) in 2016 [1]. From 2006 to 2016 studies reported an increase of 18% and 21.9% in YLDs for low back and neck pain, respectively. Low back pain was the leading disability across all age groups and for both genders [1]. In a retrospective database study utilizing the Humana database from 2008 to 2014, a steep increase in cervical and lumbar degenerative disorders (42% and 33% respectively) was reported [2]. Intervertebral disc (IVD) herniation or degeneration, spinal stenosis, and degenerative spondylolisthesis are the most common spinal pathologies that lead to neck and low back pain. Disc herniation contributes to the onset of pain by nucleus pulposus displacement and compression of the spinal cord or nerves. In addition, a local increase in pro-inflammatory markers further aggravates the pain. Patient comorbidities and other risk factors can contribute to the onset and magnitude of pain. The Spine Patient Outcomes Research Trial (SPORT) analyzed the prevalence of the most common degenerative disorders and reported that 52.4% of patients were diagnosed with disc herniation [3]. Patients with herniation were on average two decades younger (41.4 ± 11.2) than patients diagnosed with spondylolisthesis or stenosis. In addition, their pre-operative Oswestry Disability Index (ODI) and 36-Item Short Form Health Survey (SF-36) scores were worse than the other two groups, presenting with more pain and disability [3]. Concomitant joint disease, depression, hypertension, and stomach problems were the main risk factors among disc herniation patients.

Spine pathologies are often treated with conservative approaches including physical therapy, pain medication (opioids, non-steroidal anti-inflammatory drugs, muscle relaxants, or anti-depressants), and steroid injections. For cervical pathologies including axial pain and radiculopathy, non-operative strategies have shown positive results [4]. Among disc herniation patients in the SPORT study, a higher utilization of physical therapy, chiropractic care, anti-depressants, and opioids was seen when compared to patients with spinal stenosis or spondylolisthesis [3]. Complex pathologies and

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failed conservative treatments will ultimately lead to a surgical procedure. Spine fusion with or without discectomy has been the most commonly used approach. Tosteson et al. reported that patients with disc herniation who underwent surgery had better QALY improvements compared to non-surgical patients (3.24 vs 2.9) over a four year follow-up [5]. A cost reduction in the overall care was observed over a four year follow-up compared to non-surgical patients. In addition, revision rate among patients with disc herniation was 8.9% [5]. These benefits of a surgical approach were also reported by Parker et al. where conservatively treated disc herniation patients did not achieve substantial improvements in quality of life or pain, and 34% underwent a surgical procedure [6].

The objectives of this narrative review are to describe the changes occurring during disc degeneration, to discuss new directions in surgical treatment of spine pathologies including disc herniations, and to examine the current evidence for IVD biologics.

Intervertebral disc pathology—a vicious circle

IVD represents a very complex joint in terms of cellular, biochemical, and mechanical elements. It is the largest acellular and avascular organ, characteristics which result in a hypoxic environment. IVDs consist of the annulus fibrosus and the nucleus pulposus, and are connected to the endplates. The annulus and nucleus are the main mechanical components of the disc, absorbing and transmitting loads along the spine vertebrae [7]. The endplate acts as a clamp holding the annulus and nucleus together and is the main nutrient transport site. Each component is supported by very distinct cell types, which are fibroblast-like in annulus, chondrocyte-like in nucleus and chondrocyte-/bone-like in the endplate [8]. Stairmand et al. demonstrated that disc cells are not equally distributed throughout the tissue, the highest concentration was close to the endplates and the distribution was influenced by changes in oxygen concentration [9]. The presence of specific cell types is reflected by distinct matrix components in the annulus and the nucleus. Collagen I is the primary matrix protein in the annulus, while collagen II and proteoglycans (aggrecan in particular) are key constituents of the nucleus.

Despite the considerable world-wide prevalence of IVD degeneration and low back pain, little is known about the underlying cellular pathophysiology of those conditions. Aging has been identified as a primary factor of disc degeneration. However, gene alteration, environmental factors and psychosocial factors are important contributors to the onset of spine pathologies [8, 10]. Changes in loading and the nutrient supply lead to apoptosis and the secretion of pro-inflammatory cytokines and matrix metalloproteinases within the disc tissue [11]. In addition to releasing inflammatory mediators, disc cells have the ability to produce angiogenic and neurogenic molecules [12]. The inflammatory process is a major contributor to the changes in the hydrophilic matrix of the IVD and eventually leads to irreversible structural damage. Preservation of the annulus, in particular the outer layer, is crucial for prevention of disc herniation. Annular tears, cell apoptosis, and fibrosis of the nucleus trigger changes in the outer annulus accelerating the onset of herniation. It is important to understand that disc herniation is a protrusion of the entire disc structure, not only the nucleus. Roberts et al. found that 34% of herniation samples were composed of annulus, 34% had nucleus and 32% contained both tissues. In addition, 20% of the samples contained endplate particles within the protruded space [13].

Structural changes in the disc joints result in an altered load distribution, further affecting the annulus and nucleus, and leading to instability. Although the compression forces are essential for IVD metabolism, their type and magnitude have been correlated with the progression of degenerative cascades. Lotz and co-workers demonstrated that in mouse discs, an increase in static compression loading had a significant impact on the cellular and biomechanical properties [14]. Both collagen and aggrecan responded to loading. However, collagen II was more sensitive to all loading intensities. Short-term compression load had a negative impact on the restoration of cell numbers but not disc structure, while long-term load showed an irreversible impact on both cellular and structural components [14]. Although the relationship between biomechanics and disc degeneration is complex, joints possess hypermobility during the initial stages of degeneration that diminishes in later stages. This results in limited motion, causing pain and disability [15]. Given that the majority of disc herniations occur posteriorly or posterolaterally, any changes in rotation and higher torque will have a large impact on the disc and the surrounding tissues in load transmission.

Tools for regeneration

The primary goal of any spine treatment is the restoration of function and the reduction of pain. Depending on the patient's background, both biological therapies and spine fusion could fulfill those goals. In addition to spine fusion, artificial disc replacement and laminectomies with discectomies are used for the treatment of disc herniations.

Surgical options

New technologies in spine fusion

Iliac crest bone graft (ICBG) has remained the gold standard for promoting spinal fusion. However, donor site morbidity remains a substantial drawback. Consequently, the use of

allograft and synthetic bone substitutes have gained in popularity. Unfortunately, high quality data comparing the efficacy of various biomaterials in the setting of spine surgery is limited. Many existing studies report on outcomes following variable combinations of autologous bone, allograft, and/or synthetic utilization, which limit specified analysis. Inevitably, ICBG continues to remain the gold standard when comparing fusion rates. However, most of the aforementioned alternatives have demonstrated acceptable fusion outcomes. [16–18].

Technological advancements in the development of new biomaterials have recently abounded. Collagen- or polyester-based scaffolds that allow for fine tuning of respective mechanical properties and the biocompatibility profile to promote spinal fusion or to optimize growth factor delivery have shown promise in animal studies [19–21]. More recently, biomimetics such as P-15 have demonstrated favourable fusion rates in early clinical studies in the setting of anterior cervical discectomy and fusion (ACDF) and anterior lumbar interbody fusion [22, 23].

The limited biocompatibility of traditional polyetheretherketone (PEEK) interbody implants has been a long-standing concern [24]. With use of PEEK, successful fusion has often relied on utilization of osteoinductive and osteoconductive adjuncts. Resultantly, titanium (Ti)-coated PEEK cages have emerged to combine the more biocompatible Ti while maintaining the more optimal material properties and imaging-friendly traits of traditional PEEK implants. Both pre-clinical studies and early clinical studies are encouraging, with increased rates of osseointegration and improved pull-out and push-out strength with use of Ti-coated PEEK when compared to traditional PEEK interbody devices [25, 26]. More recent evidence suggests that modification of the flat surface topography of traditional PEEK may encourage even more robust osseointegration than Ti-coated PEEK [27].

3-dimensional (3D) printing has been applied to interbody technology. This technology allows for the creation of implants with customizable stiffness and porosity which enables more optimal osseointegration [28, 29]. While early pre-clinical data shows promise, high-quality clinical studies are currently lacking.

Cervical disc arthroplasty

Cervical disc arthroplasty (CDA) was first approved for use in the USA by the Food and Drug Administration (FDA) in 2007 for the surgical management of radiculopathy or myelopathy secondary to one or two-level cervical disease. As a motion preserving technology, CDA was originally developed as an alternative to ACDF in an effort to better preserve the natural biomechanics of the cervical spine.

Mid- to long-term CDA data has demonstrated significantly reduced rates of adjacent segment degeneration (ASD) and need for secondary surgeries when compared to ACDF [30, 31]. In their seven year follow-up study, Janssen et al. reported a 7% rate of secondary surgeries in the CDA group compared to 18% in the ACDF group ($p = 0.0099$) with 92% patient follow-up [16]. A recent review of nine clinical trials that evaluated rates of re-operation secondary to symptomatic ASD reported that 3.1% of patients with previous CDA required a re-operation compared to 6.0% of patients with previous ACDF at up to 80-month post-operative follow-up [32].

With short-term follow-up, patient-reported outcomes appear to be equivalent between CDA and ACDF. A recent review, which included 14 randomized controlled trials, determined that 50% of studies reporting neck disability index and SF-36 physical components scores favored CDA over ACDF at four to seven year follow-up. Additional benefits of CDA include improved range of motion and decreased rates of dysphagia when compared to ACDF [33].

Although data is currently limited, similar positive findings have been demonstrated in the setting of two-level CDA and multi-level CDA [34]. More recently, hybrid surgeries which combine CDA with fusion have gained popularity for the management of multi-level cervical disease. Early results are promising, with improvements in short-term outcomes and post-operative cervical motion when compared to fusion alone [35, 36]. In addition, Radcliff and co-authors reported that CDA was a cost-effective approach for management of single-level cervical disease [37]. Longer term data will offer further insight into the utility of CDA as well as the life-expectancy of these implants.

Navigation and robotics

Computer-assisted navigation (CAN) in spinal surgery has become increasingly popular. Not only has CAN been shown to substantially decrease radiation exposure to the surgeon, operating room staff, and patient when compared to fluoroscopic assisted surgery [38], it has been shown to enable more accurate pedicle screw placement. Interestingly, the latter technical benefit has not translated into any clinically meaningful differences in rates of associated complications [39, 40]. A recent review article found a 6% perforation rate for navigated screws when compared to 15% for free-hand screws. While no navigated screws resulted in a complication, the overall rate of neurological complications in the free-hand group was only 0.08% [39]. Improved accuracy with pedicle screw placement may be of even more value in the setting of cervical spine surgery [41]. Pedicle screws in the cervical spine have been shown to improve the overall construct strength when compared to lateral mass screws [42]. CAN shows similar promise in the setting of complex revision surgery as it allows for optimal screw size selection, enhancing the biomechanics of screw fixation [43].

Currently, there are three robotic systems that are FDA approved for robotic-assisted pedicle screw guidance.

Similar to CAN, robotic-assisted surgery has been shown to improve the accuracy of screw placement and reduce overall radiation exposure when compared to fluoroscopic-assisted surgery [44]. Lack of fatigability, improved dexterity, and surgical precision, particularly when navigating through a small surgical portal, are additional benefits of robot assistance. Rates of associated complications are low, and robot assistance has additionally been associated with shortened postoperative lengths of stay [44]. With an upfront cost of $850,000 and up to $2000 of yearly maintenance, the cost benefit of robotic-assisted surgery remains to be determined. Further, the use of a robotic arm certainly does not completely prevent screw misplacement [45]. Consequently, diligent oversight by the operating surgeon is still warranted to mitigate the risk of serious complications.

Disc biologics

Biological strategies include scaffold implants, cell-based therapies, growth factor injection, and gene therapy. Biological interventions are aimed at slowing down the rate of degeneration and senescence, induction of regeneration, enhancement of viability and matrix production of surviving cells, and eventually restoration of mechanical properties of IVD. Even though some of these biological therapies have undergone human trials, their clinical application is limited by safety concerns inherent to biological interventions, lack of evidence for sufficient effectiveness, or lack of sustained effect.

Route of injection: annulus versus endplate

Delivery of therapeutics to IVD is challenging and the optimal approach is an ongoing debate. Most biological interventions on IVD are focused on restoration of nucleus. Therefore, therapeutic agents are conventionally injected using the transannular approach. This method has recently been criticized based on the evidence emerging from discographic and experimental studies [46, 47]. Annular injury is a common procedure for mechanical induction of disc degeneration in animal models [48, 49]. Thus, the injury induced by needle puncture may initiate a cascade of biomechanical changes resulting in degeneration as a side effect of biologic interventions [50]. Furthermore, it has been suggested that the leakage of material through punctured annulus may expose the tissues in vicinity of injection site to bioactive agents, resulting in aberrant osteophyte formation or potentially dangerous side-effects [51]. More recently, trans-endplate injection has been suggested as a route for delivery of biological material, which preserves the integrity of annulus at the expense of endplate damage [52, 53]. There is limited in vivo evidence on safety of this approach, showing that complications associated with trans-endplate approach are rare but serious [52]. Considering the central role of endplate in IVD homeostasis, it is not surprising that iatrogenic damage of endplate may put IVDs at risk of nutritional distress, which in turn may result in degenerative changes.

Nucleus pulposus scaffolds

Scaffolds are used as standalone injectable treatments or as carriers of cell-based therapies. Water is the main constituent of healthy nucleus and dehydration is a key finding following degenerative changes. Loss of nucleus water content not only affects the mechanical properties of IVD, but also causes imbalance in the microenvironment surrounding the cells [54]. Therefore, hydrogel scaffolds have been suggested as suitable substitutes for degenerated nucleus. Synthetic scaffolds, such as polyurethane and polyglycolic acid are targeted at structural reinforcement and restoration of mechanical function, while natural hydrogels such as hyaluronic acid, fibrin, collagen, and gelatin are advantageous in mimicking the natural microenvironment of nucleus. Decellularized extracellular matrix is a physiologically relevant subtype of scaffolds that closely resembles the native nucleus pulposus matrix in terms of cyto compatibility and 3D structure [55–59]. Decellularized matrix has been shown to induce new extracellular matrix production, and to enhance the viability of stem cells when used as a cell-laden scaffold [57, 59]. In situ polymerization is an interesting concept that has been employed for both naturally-occurring and synthetic scaffolds [60]. Furthermore, in situ hydration of so called dry scaffolds is claimed to make them functionally analogous to naturally occurring glycosaminoglycans by means of dynamic maintenance of the water content [60, 61].

Annulus fibrosus scaffolds

Annular tearing is a well-known entity in the process of symptomatic IVD herniation. Surgical options are available for repair of the annular defect, some of which have been successful in short-term prevention of disc re-herniation [62]. Similar to nucleus, various injectable hydrogels are among the options suggested for biological treatment of annular defect. Methacrylated gellan-gum is an injectable hydrogel that has been used in combination with cellulose nanocrystals. This combination sustained the cell viability in bovine annulus fibrosus culture model, and mechanically approximated the characteristics of human annulus fibrosus owing to its crosslinking capability [63]. Mechanical properties of annulus fibrosus are highly dependent on complex laminar orientation of its elastic fibers. Hence, bioengineered annulus fibrosus scaffolds require special design considerations. A multilayered scaffold consisting of polycaprolactone fibers reinforced with glue and fascia has been used in porcine model

of surgical annular repair [64]. This method was successful in achieving normal organization of de novo collagen fibers [64]. Despite these advancements, annulus fibrosus scaffolds are still in experimental phase and biological regeneration of annulus remains an expanding area of research.

Cell-based therapy

Primary IVD cells and stem cells derived from different sources, such as adipose tissue, bone marrow, and synovium are the cornerstone of cell-based therapies. Interestingly, comparison of stem cells isolated from degenerated human nucleus pulposus tissue with bone marrow stem cells has shown comparable characteristics in terms of pluripotency and morphology, rendering native nucleus pulposus stem cells a novel source of cell-based therapy [65]. Stem cells not only improve the anabolic activity of nucleus cells, but also express immunomodulatory effects that suppress the inflammatory responses associated with IVD degeneration [66, 67]. However, harsh microenvironment of the IVD is a key-limiting factor for survival of transplanted stem cells [66]. A small case series of patients undergoing lumbar intradiscal stem cell injection showed a decrease in degeneration score based on magnetic resonance imaging in 40% of the patients at one year, and improvement of pain and disability scores at three years [68]. Still, similar to other biological treatments, sustainability of the effects is a relevant aspect of cell-based therapies which needs to be addressed.

Growth factors

Parallel to the growing application of bone morphogenetic proteins (BPMs) in spinal fusion and other orthopaedic procedures, these members of the transforming growth factor beta (TGF-b) superfamily have been extensively investigated for their regenerative potential in IVD. BMPs have shown anti-apoptotic effects on nucleus cells and anabolic stimulation by maintenance or upregulation of ECM production in rabbit and human experimental models [69–71]. Although these effects were confirmed in vitro for recombinant BPM-7 in canine model, intradiscal injection of this growth factor did not sustain the regenerative effects in canine spontaneous disc degeneration model and resulted in focal sclerosis and bone formation [72]. Activated platelet-rich plasma (PRP) works as a concentrate of multiple growth factors such as insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), TGF-b, and basic fibroblast growth factor (bFGF). Following the promising findings of experimental studies, intradiscal PRP injection has been assessed in a prospective human trial, showing short-term improvement of patient-reported outcome measures such as pain and function compared to controls [73]. Nevertheless, robust randomized trials are still needed to elucidate the safety and long-term efficacy of intradiscal PRP injection [74].

Conclusions

While fusion surgery has traditionally been the treatment of choice for IVD degeneration and herniation, disc replacement and discectomy are gaining increasing interest. Patient comorbidities and revision surgery still represent one of the main challenges. The economic burden of spine degenerative disorders is very complex and has yet to be addressed. The majority of studies have focused on direct or total cost of spine pathology, often disregarding indirect and intangible costs. It remains to be seen if alternative surgical approaches and robotic assistance will be able to provide better outcomes and a reduced financial burden than spine fusion. Non-invasive biological interventions, such as cell- and protein-based therapies hold great promise; however, solid preclinical evidence is still lacking. A successful biological treatment will have to deliver significant clinical benefit in pain reduction and restoration of functional IVD unit.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest. Disclosures outside of submitted work: ZB—consultancy: Xenco Medical, AO Spine; research support: SeaSpine (paid directly to institution); JCW—Royalties—Biomet, SeaSpine, Amedica, DePuy Synthes; Investments/Options—Fziomed, Promethean, Paradigm Spine, Benvenue, Nexgen, Vertiflex, Electrocore, Surgitech, Expanding Orthopedics, Osprey, Bone Biologics, Pearldiver; Board of Directors—North American Spine Society, North American Spine Foundation, AO Foundation, Cervical Spine Research Society; Fellowship Funding (paid to institution): AO Foundation.

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